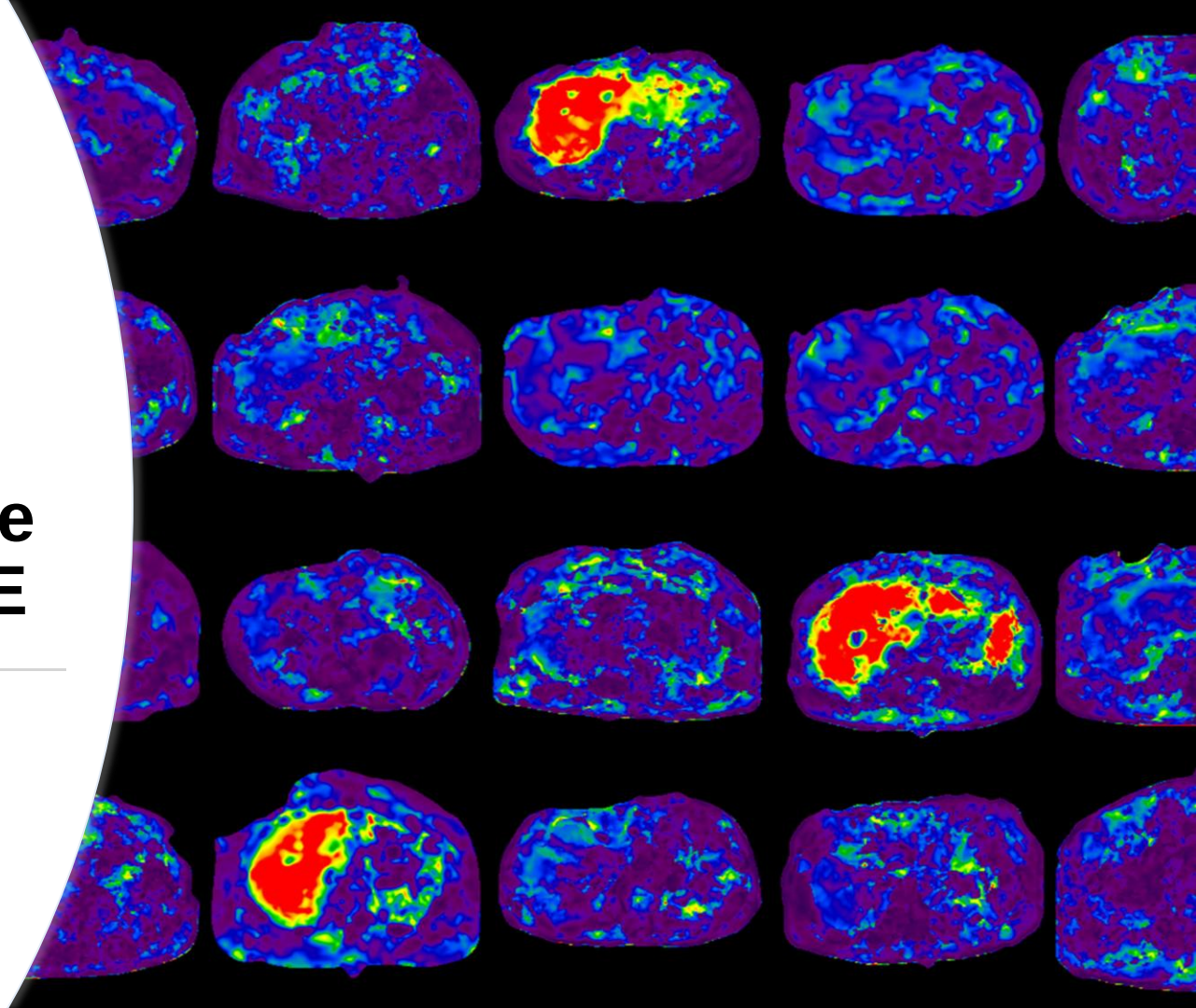
Non-Invasive Tests for Reasonably-Likely Surrogate Endpoints: MRE

Kay Pepin, PhD



Disclosure

- Kay Pepin is an employee of Resoundant, Inc.

Background and scope

2,500+ Installations Worldwide

- Liver Stiffness Measurement (LSM) is a direct measure of an intrinsic, mechanical property of the liver
- LSM by MRE
  - Well-established in routine clinical practice
  - Widely available globally, especially in the US
  - Has a large body of clinical evidence on its usefulness for the for the management of patients with MASLD
  - Recommended in numerous guidelines (AGA, ACEE, AASLD, ACR, APASL, EASL,…)

Goal of today's presentation is to review the latest clinical evidence supporting the use LSM by MRE as a Reasonably Likely Surrogate Endpoint in MASLD/MASH by focusing on:

- Accuracy in baseline staging
- Prognosing clinical outcomes
- Monitoring clinical outcomes
- Monitoring treatment response

5 Criteria for a RLSE (Reasonably Likely Surrogate Endpoint)

Biological Plausibility

- The surrogate must reflect a **core biological process** that drives disease progression.

Predictive Value for Clinical Outcomes

- Changes in the surrogate should **strongly correlate** with meaningful outcomes (e.g., cirrhosis, death).

Consistency Across Studies and Therapies

- The marker should be **reliable across different drugs, trials, and patient populations.**

Standardization and Reproducibility

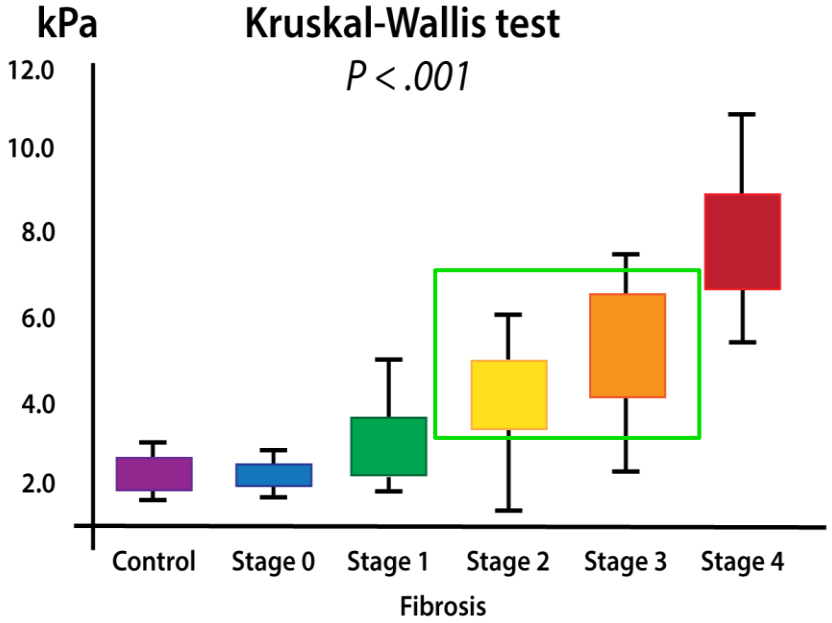
- It must be **accurately and consistently measured** across sites, vendors, and timepoints.

Feasibility in Pivotal Trials

- The test must be **practical, scalable, and interpretable** in large multicenter clinical trials.

1. MRE: Biologic Plausibility

Directly reflects fibrosis burden: MRE quantifies liver stiffness, which correlates with collagen deposition and extracellular matrix remodeling — the core pathophysiologic driver of fibrosis progression.

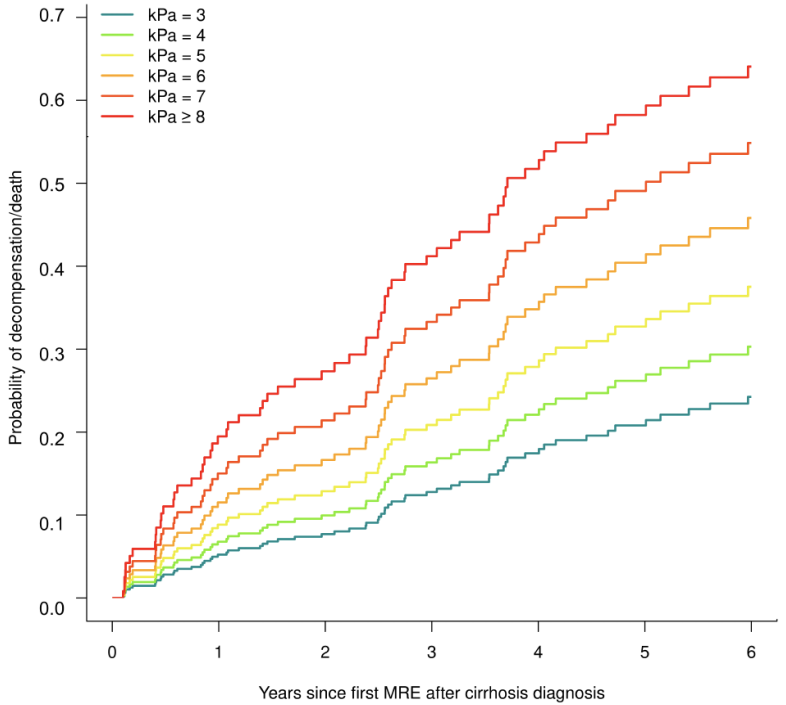


Adapted from Imajo et al. Gastroenterol (2015) 150(3):626-637.

2. MRE: Predictive Value for Clinical Outcomes

Strong predictor of progression to cirrhosis
MRE values ≥4.0 kPa are independently associated with increased risk of developing cirrhosis within 3–5 years — even after adjusting for histologic stage and lab markers.

Quantitatively forecasts liver-related events (LREs)
Higher baseline and rising serial MRE values predict key outcomes: hepatic decompensation, variceal bleeding, liver cancer, and need for transplant.



Gidener et al (2021) *Clinical Gastroenterology and Hepatology*; Vol 19, Issue 0, P1915-1924

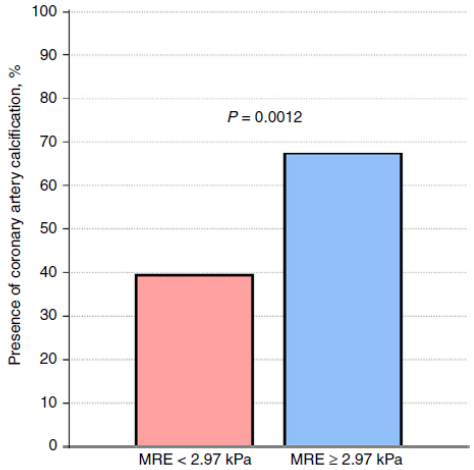
Risk of cardiovascular disease

DOI: 10.1111/apt.16324

APT Alimentary Pharmacology & Therapeutics WILEY

Liver stiffness by magnetic resonance elastography is associated with increased risk of cardiovascular disease in patients with non-alcoholic fatty liver disease

Jung Gil Park[1,2] | Jinho Jung[1] | Kritin K. Verma[1] | Min Kyu Kang[2] | Egbert Madamba[1] | Scarlett Lopez[1] | Aed Qas Yonan[1] | Amy Liu[1] | Ricki Bettencourt[1] | Claude Sirlin[3] | Rohit Loomba[1,4]

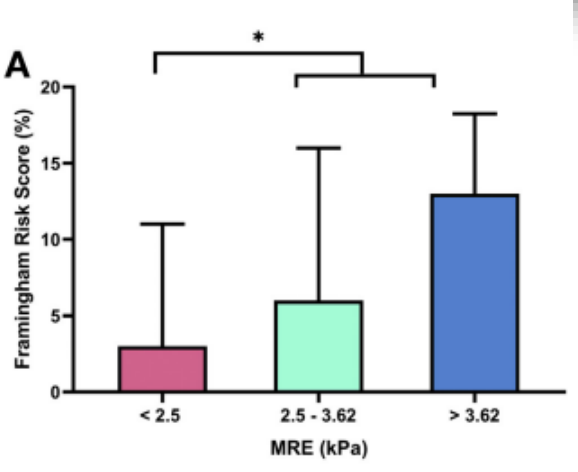


Clinical Gastroenterology and Hepatology 2020;18:744–746

Liver Stiffness Severity is Associated With Increased Cardiovascular Risk in Patients With Type 2 Diabetes

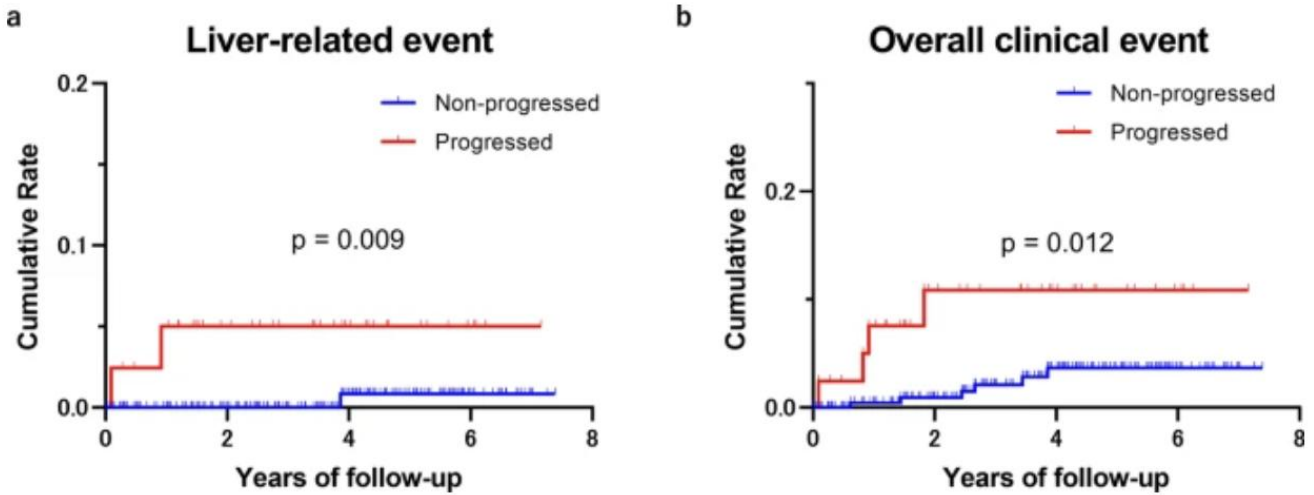
Neeraj Mangla,* Veeral H. Ajmera,*,‡ Cyrielle Caussy,*,§ Claude Sirlin,‖ Sharon Brouha,‖ Sonia Bajwa-Dulai,* Egburt Madamba,* Ricki Bettencourt,* Lisa Richards,* and Rohit Loomba*,‖,¶

*NAFLD Research Center, Department of Medicine, La Jolla, California; ‡Division of Gastroenterology, Department of Medicine, La Jolla, California; §Université Lyon 1, Hospices Civils de Lyon, Lyon, France; ‖Liver Imaging Group, Department of Radiology, University of California at San Diego, La Jolla, California; and ¶Division of Epidemiology, Department of Family and Preventive Medicine, University of California at San Diego, La Jolla, California



Serial MRE tracks treatment impact

- Increases in MRE stiffness over time are associated with increased hazard for liver-related events
- Decreases in MRE are *reasonably likely* to be associated with decreased hazard for liver events — supporting its use for longitudinal risk stratification.



Kobayashi, *et al. J Gastroenterol* (2023). https://doi.org/10.1007/s00535-023-02049-9

3. MRE: Consistency Across Studies and Therapies

Reproducible across multiple large MASLD/MASH cohorts
MRE thresholds (e.g., ≥3.6 kPa for F2–3 fibrosis) consistently correlate with biopsy-confirmed fibrosis across academic, community, and international sites.

Convergent findings in different therapeutic trials
MRE has shown similar dynamic response patterns to fibrosis-directed therapies — including FXR agonists, THR-β agonists (e.g., resmetirom), and GLP-1s — across Phase 2 and 3 studies.

Independent and broadly validated technology
MRE was developed at Mayo Clinic and shared widely with researchers; it is not a proprietary platform. Many validation studies are independently conducted.

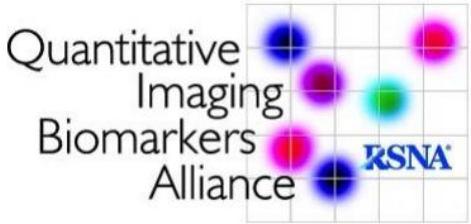
4. MRE: Standardization and Reproducibility

Uniform acquisition protocol across vendors and scanners
2D MRE uses a standardized pulse sequence and processing pipeline, developed by the RSNA QIBA, that is harmonized across all major MRI platforms (GE, Siemens, Philips), minimizing variability.

High intra- and inter-reader reproducibility
Studies show MRE has extremely low coefficient of variation (~5–7%) and excellent intra/inter-observer agreement, even across different institutions.

Minimal operator dependence
Unlike ultrasound-based methods, MRE requires no manual probe placement or user adjustments, reducing human error and enhancing reproducibility.

Consistent results across BMI and liver disease etiologies
MRE retains accuracy and reliability even in patients with high BMI or hepatic steatosis, unlike modalities whose reproducibility suffers in these populations.



5. Feasibility in Pivotal Trials

Routinely implemented at 2,500+ global sites
MRE is currently used in large multicenter trials across North America, Europe, and Asia, with standardized protocols ensuring consistent data collection.

Short scan time and standalone workflow
MRE+PDFF can be performed as a 10–15 minute standalone scan, minimizing patient burden and scanner time — especially important in trial logistics and enrollment.

Supported by trained central readers and imaging CROs
Major imaging CROs are experienced in MRE central reading, which avoids operator subjectivity; MRE images are compatible with standard DICOM workflows, enabling scalable and compliant trial execution.

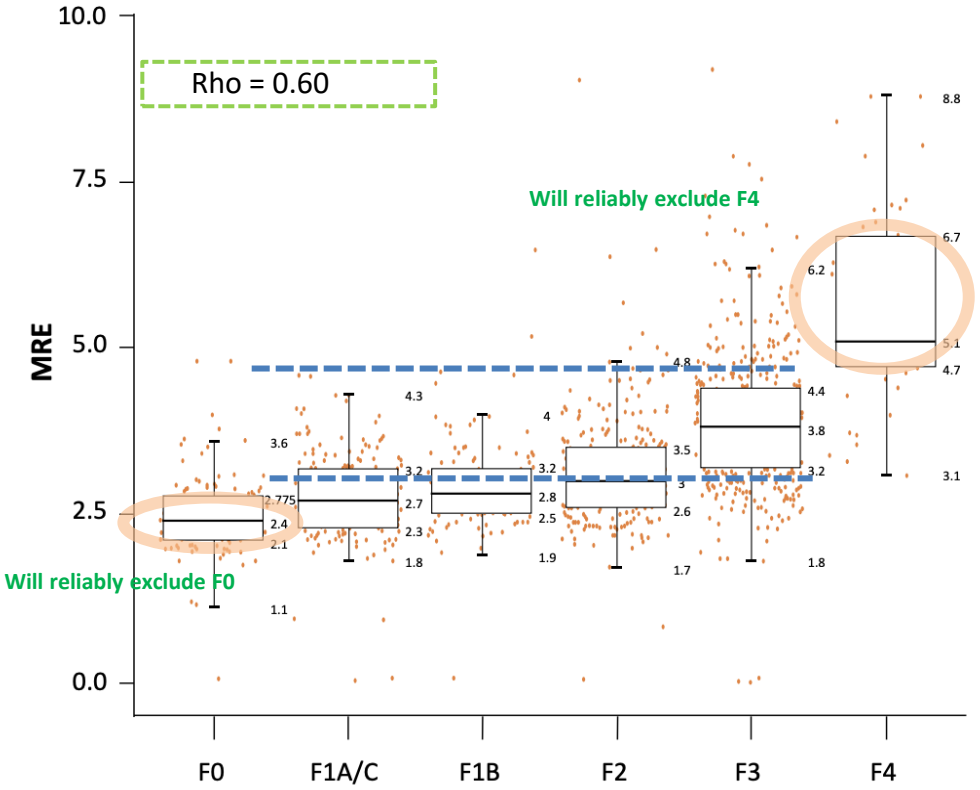
REAL-WORLD EVIDENCE AS A RLSE:

STAGE F2-F3 ACCURATELY

MONITOR TREATMENT RESPONSE RELIABLY

STAGE F2-F3 ACCURATELY

MRE in MAESTRO-NASH



MRE

- 75th and 25th quartiles for F2-F3:
  - Perfect exclusion of F4
  - Also excludes F0
  - Includes about half of F1 patients, though given the challenges for reliable histologic scoring of these patients, their treatment/inclusion would likely be acceptable

"One of the key findings of this study is the clinical validation in the setting of a clinical trial that MRE provides the highest accuracy and positive predictive value for detecting patients with NASH and stage 2 or 3 fibrosis who need pharmacologic therapy," Loomba said.

Source: Loomba R, et al. Abstract 102. Utility of FIB-4, MRE, MRI-PDFF and FibroScan to identify patients with at-risk F2-F3 NASH based on screening data from a 2,000-patient biopsy confirmed cohort of resmetirom phase 3 clinical trial, MAESTRO-NASH. Presented at: The Liver Meeting; Nov. 4-8, 2022; Washington (hybrid).

VCTE in MAESTRO-NASH

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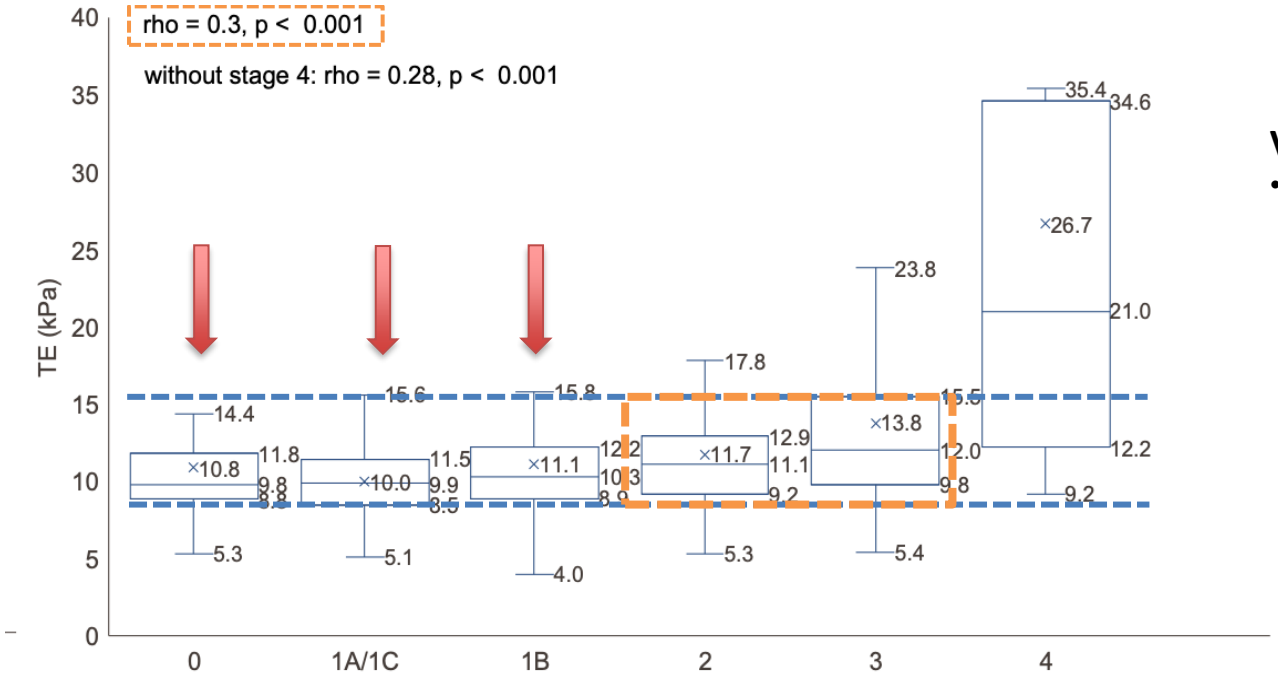
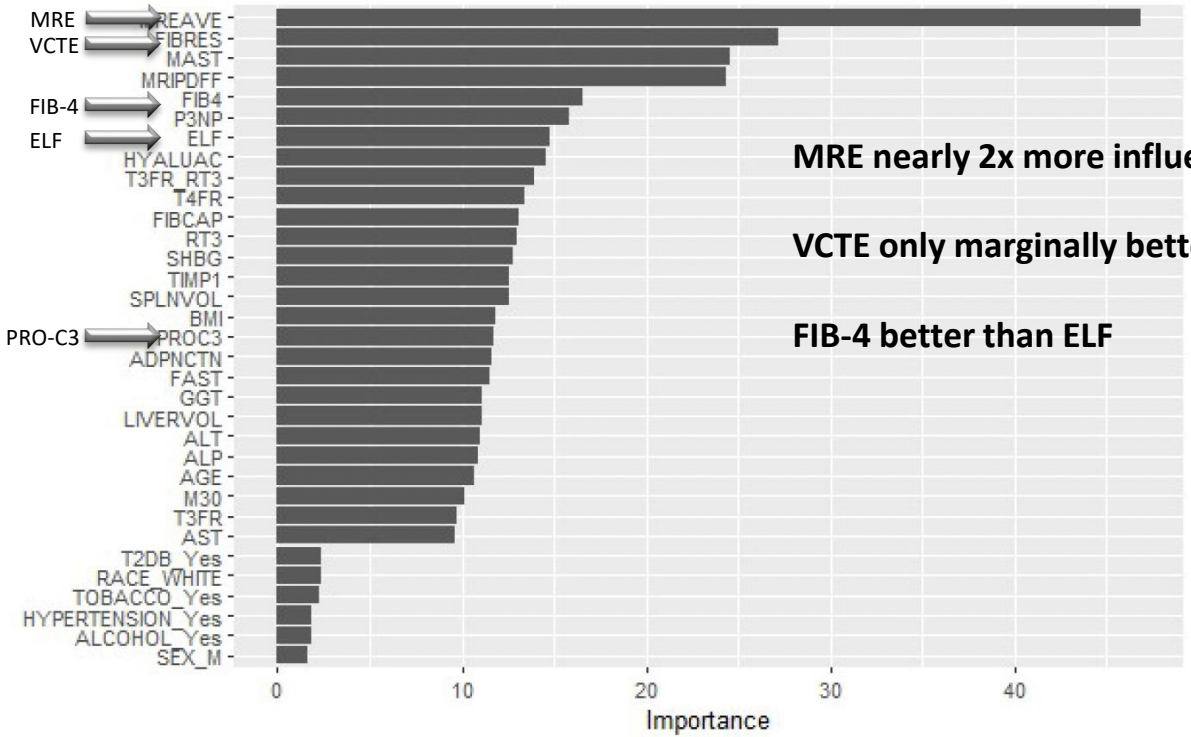


VCTE

- 75th and 25th quartiles for F2-F3:
  - Minimal overlap of F4
  - **But captures almost all F0 and F1 patients – lack of specificity results in too many false positives**
  - Might be best reserved for identifying cirrhotic patients only (drugs in development)

Influential Biomarkers and Imaging to Predict Baseline Fibrosis Stage[1]



MRE nearly 2x more influential than VCTE

VCTE only marginally better than PDFF

FIB-4 better than ELF

[1]Based on the Random Forest Model

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MONITOR TREATMENT RESPONSE RELIABLY

Radiology

ORIGINAL RESEARCH · GASTROINTESTINAL IMAGING

Repeatability of MRI Biomarkers in Nonalcoholic Fatty Liver Disease: The NIMBLE Consortium

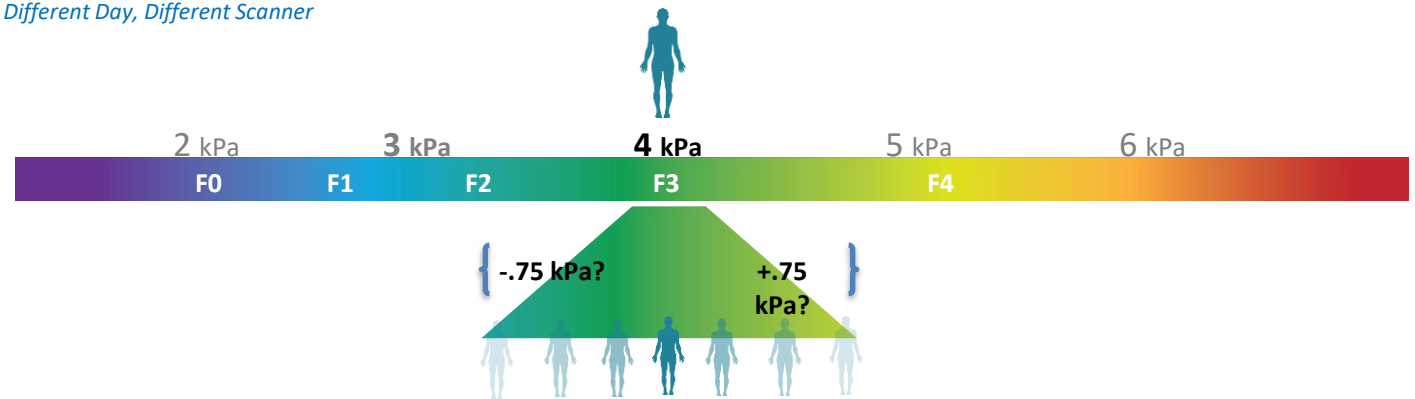
Kathryn J. Fowler, MD • Sudhakar K. Venkatesh, MD* • Nancy Obuchowski, PhD • Michael S. Middleton, MD, PhD • Jun Chen, PhD • Kay Pepin, PhD • Jessica Magnuson, BS • Kathy J. Brown, BS • Danielle Batakis, BS • Walter C. Henderson, BS • Sudha S. Shankar, PhD • Tania N. Kamphaus, PhD • Alex Pasek, MD • Roberto A. Calle, MD • Arun J. Sanyal, MD • Rohit Loomba, MD • Richard Ehman, MD • Anthony E. Samir, MD, PhD • Claude B. Sirlin, MD** • Sarah P. Sherlock, PhD***

MRE Variability

MRE: 0.75 kPa

Longitudinal Follow-up

Different Day, Different Scanner



A change in MRE-based liver stiffness of **0.75 kPa** or greater, represents a true biological change with a probability of greater than 95%. At a baseline stiffness of 4kPa, this range spans barely one stage of fibrosis.

Radiology

ORIGINAL RESEARCH · GASTROINTESTINAL IMAGING

Reproducibility and Repeatability of US Shear-Wave and Transient Elastography in Nonalcoholic Fatty Liver Disease

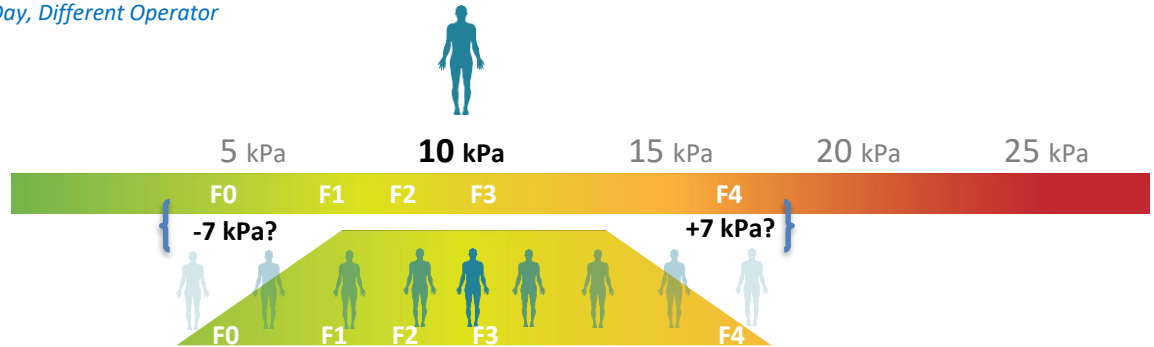
Theodore T. Pierce, MD, MPH • Arinc Ozturk, MD* • Sarah P. Sherlock, PhD • Guilherme Moura Cunha, MD • Xiaohong Wang, MD • Qian Li, MD • David Hunt, RDMS, RVT, RT(S) • Michael S. Middleton, MD, PhD • Marian Martin, MD, MPH • Kathleen E. Corey, MD, MPH, MMSc • Hannah Edenbaum, MS • Sudha S. Shankar, MD • Helen Heymann, MMSc, PMP, CPH • Tania N. Kamphaus, PhD • Roberto A. Calle, MD • Yesenia Covarrubias, MFS • Rohit Loomba, MD, MHSc • Nancy A. Obuchowski, PhD • Arun J. Sanyal, MBBS, MD • Claude B. Sirlin, MD • Kathryn J. Fowler, MD** • Anthony E. Samir, MD, MPH***

VCTE Variability

VCTE: 70%

Longitudinal Follow-up

Different Day, Different Operator



VCTE measurement displays **10 kPa**, but with 70% repeatability coefficient (NIMBLE), any longitudinal follow-up within +/- 7 kPa of the original 10 kPa average is may be attributable to instrument noise and is not sufficient to reliably represent a true biological change. This level of variability means the original measurement could also be off by multiple stages of fibrosis.

Radiology

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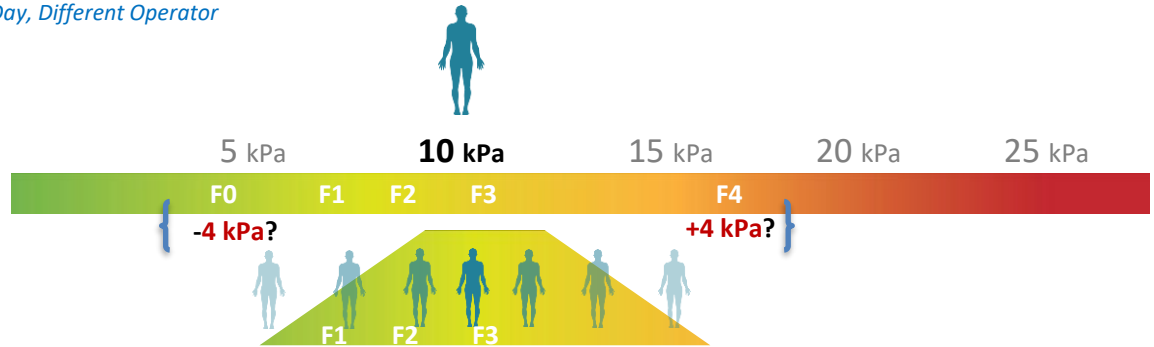
VCTE Variability

VCTE: 70%

40%

Longitudinal Follow-up

Different Day, Different Operator



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Bottom Line: RLSE Readiness

Liver stiffness is a strong biomarker for as an RLSE for fibrosis and outcomes in MASLD/MASH trials.

MRE: Strongest RLSE candidate – reproducible, standardized, and aligned with regulatory expectations.

Consider full diagnostic pathway costs, accuracy, reproducibility, operational burden, and patient-level clarity when selecting RLSEs.

Liver Forum should include MRE as a RLSE given the numerous advantages, wide availability, and ability to acquire PDFF in the same exam for no additional cost/time.